WashU Medicine

Celiac Disease: A Tail of Two HLA Alleles

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August 14, 2025

Disclosures

Worked
- Santa Ana Bio
- Omniscope

Consulted
- Epana Bio
- Starling Bio
- Columbus Instruments

Stock
- Epana Bio

Sold Software
- Columbus Instruments

None related to the topics in this presentation

Reviewing Our Reporting for Celiac Disease

Request from GI to review how we are reporting Celiac Disease HLA Typing Results.

Component	
DQB1*02 Interpretation	Negative
DQB1*03(8) Interpretation	Negative
DQA1*05 Interpretation	Positive (1 copy)

(actual patient exchange in epic)

XX

The genetics testing indicates that you have a **positive HLA DQ A1*05** with **negative HLA DQ B1*02**, thus she does not have the full HLA type that would allow you to have celiac disease.

With that said, the **test that is done at BJC is not the best test (compared to LabCorp and Quest)**. However, his suspicion for celiac disease is very low based on the information given.

Here are his suggestions:
- request the biopsies to be reviewed by our pathologists here
- **check celiac HLA DQ via LabCorp** and also check tTG IgG and gliadin IgG at the same time.

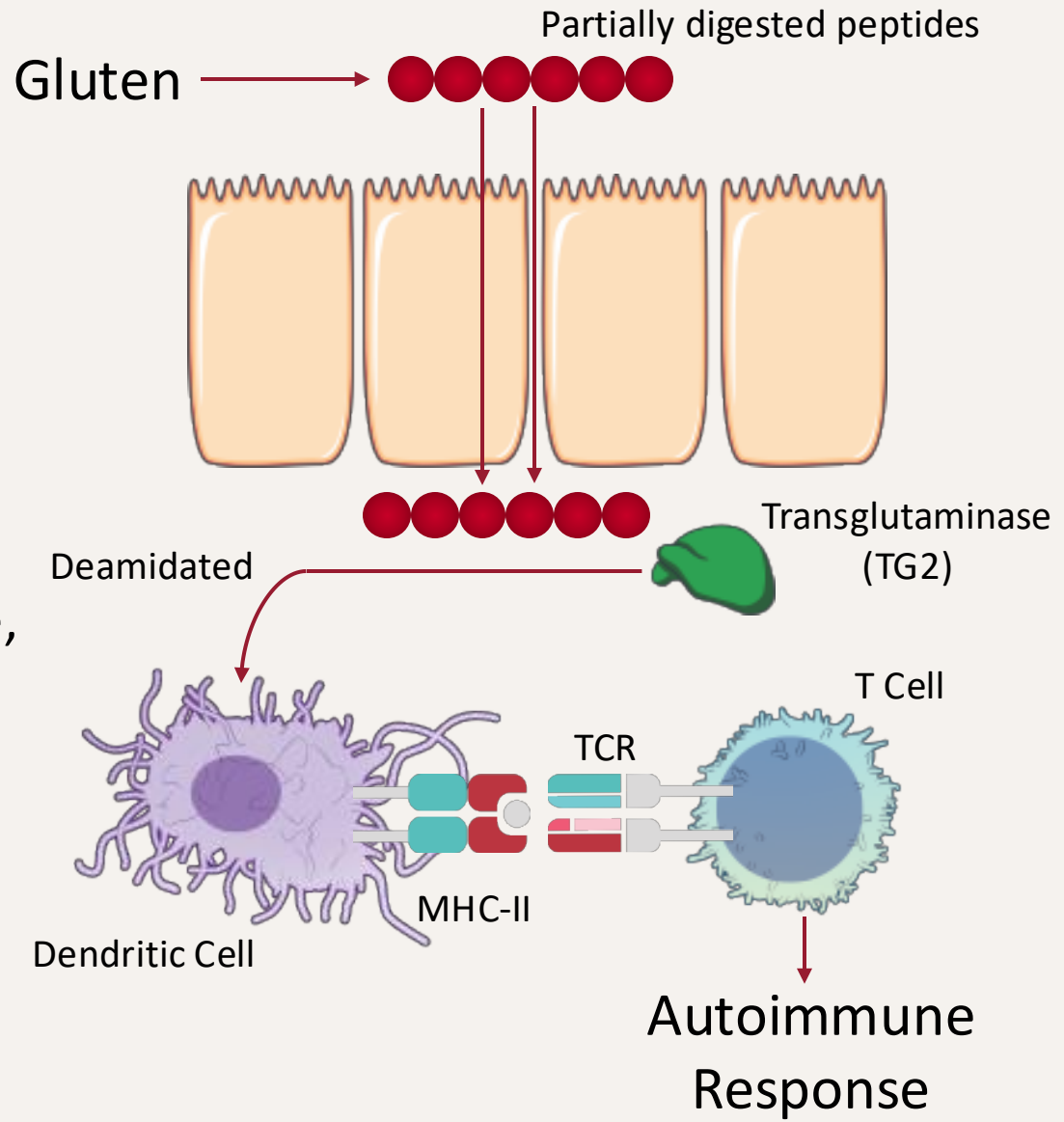
Learning Objectives

- Explain the immunopathogenesis of celiac disease, including the role of gluten peptides, tissue transglutaminase, and HLA-DQ2/DQ8–restricted T-cell activation.
- Outline the stepwise diagnostic algorithm for celiac disease, highlighting the appropriate role and timing of HLA typing.
- Interpret current approaches to HLA testing for celiac disease, including methodology, allele subtypes (DQ2.2, DQ2.5, DQ8), and clinical implications of results.

What is Celiac Disease?

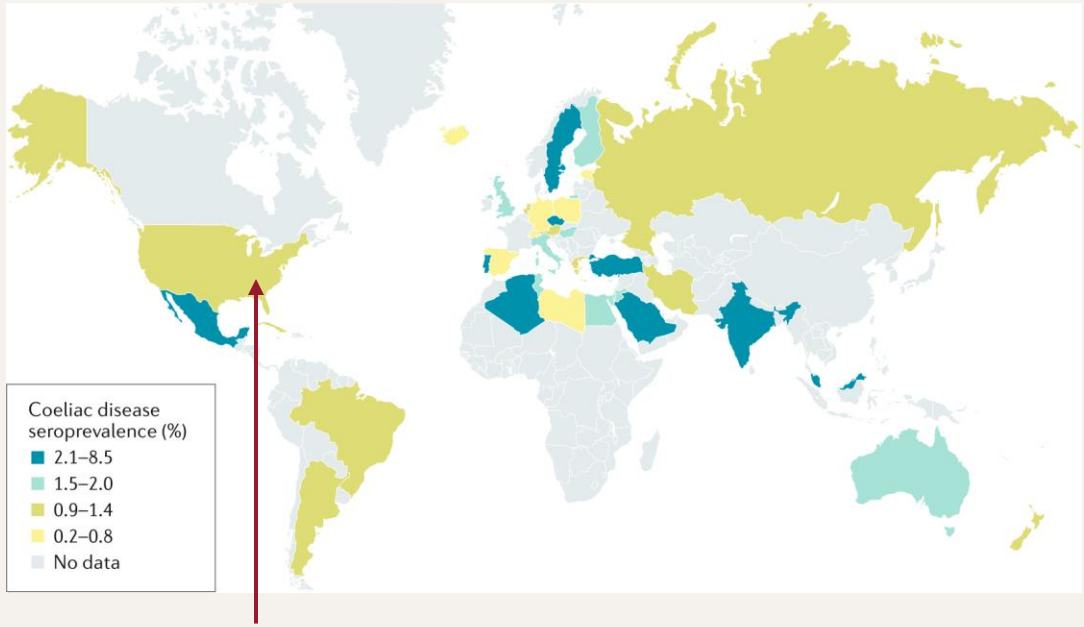
Chronic, systemic autoimmune disorder triggered by the ingestion of gluten in genetically susceptible individuals.

- **Autoimmune:** The body's immune system mistakenly attacks its own tissues.
- **Trigger:** Gluten, a protein found in wheat, barley, and rye.
- **Target:** The primary site of injury is the small intestine, leading to inflammation and damage to the intestinal lining.



Global Incidence and Prevalence

- **Global prevalence:** ~1.4% by serology; ~0.7% biopsy-confirmed
- **In the US**: One of the most common autoimmune disorder affecting **1 in 100** people
- **The "Celiac Iceberg":** Most cases remain undiagnosed—recent reviews estimate ~83–95% undetected in many countries
- **Trends:** Diagnoses have increased over decades due to both true rise and better awareness/testing



US steady rates → gluten-free diet options?

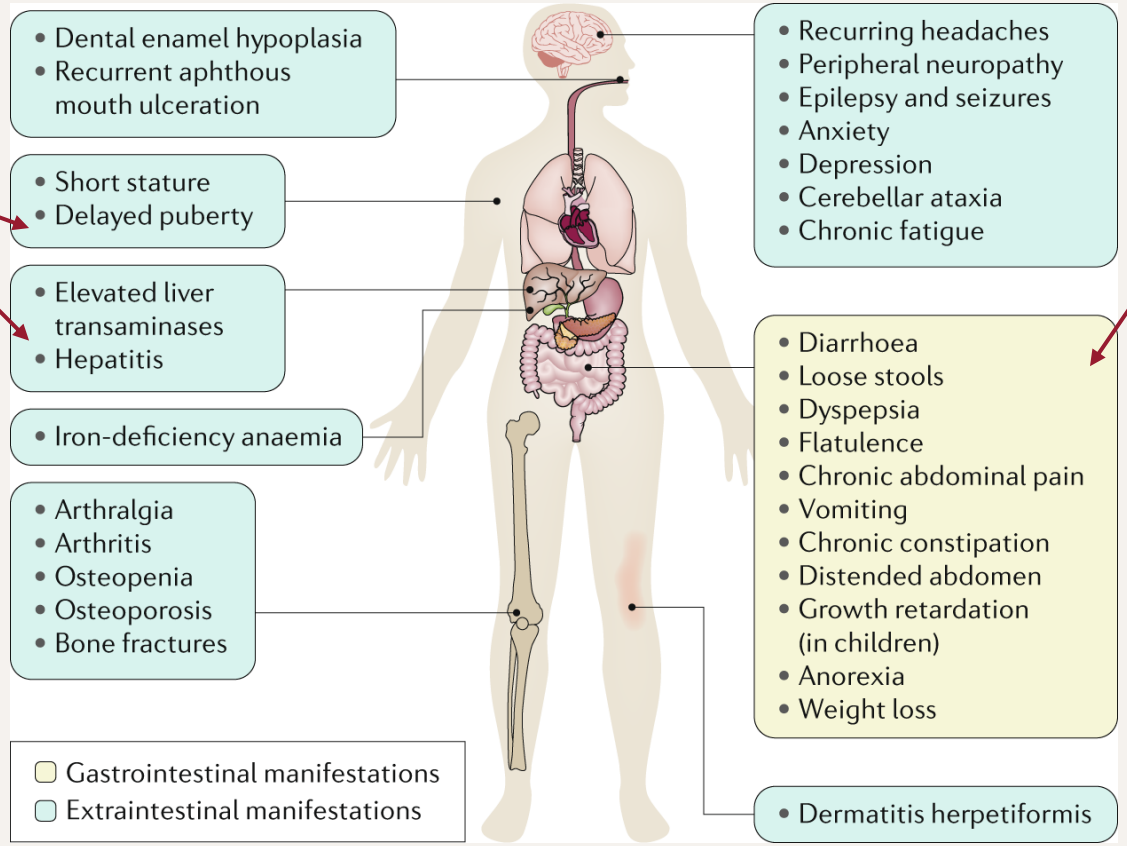
Clinical Presentation: A Spectrum of Symptoms

The presentation of celiac disease is highly variable and can manifest at any age.

Symptoms can be broadly categorized into **gastrointestinal** and **non-gastrointestinal**.

Non-gastrointestinal

Result of micronutrient deficiencies

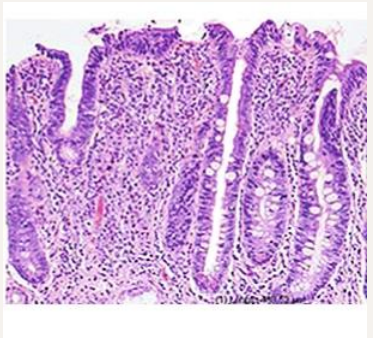


Gastrointestinal

Result of damage to GI Tract

Villous Atrophy leading to poor absorption

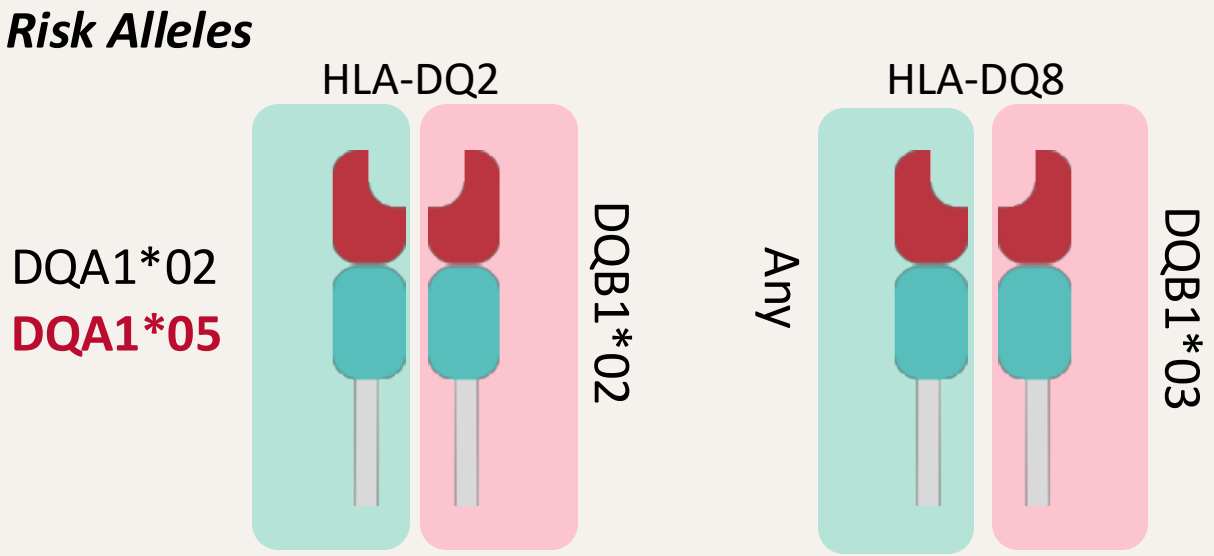
Good Villi

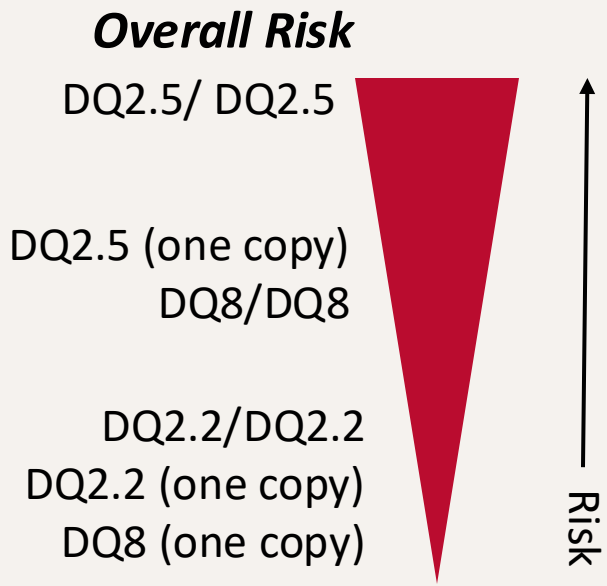


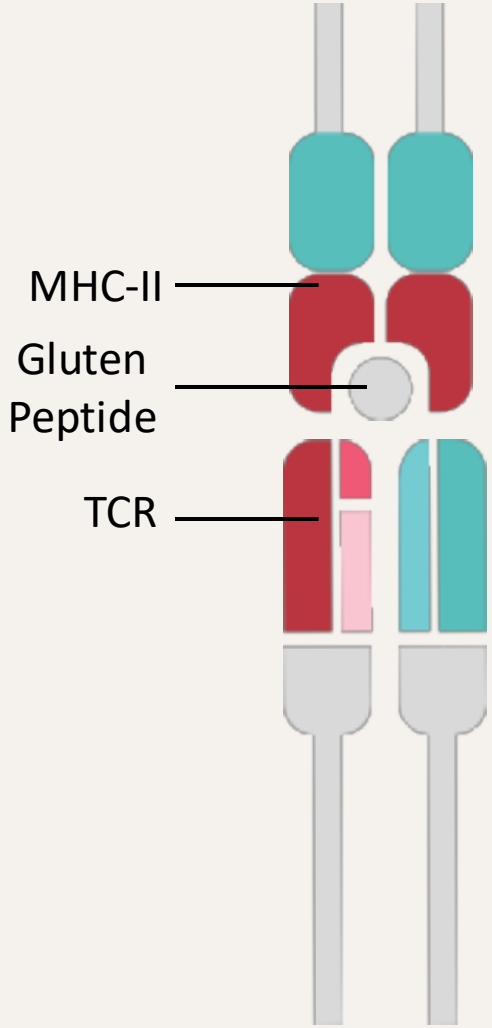
”Blunted” Villi

Genetics: Why HLA Allelic Testing Matters

- **Very strong HLA association:** >95–99% of biopsy-proven CD carries **HLA-DQ2 (DQ2.5 or DQ2.2)** or **HLA-DQ8.**
- These alleles are **necessary but not sufficient:** carried by ~30–40% of the population

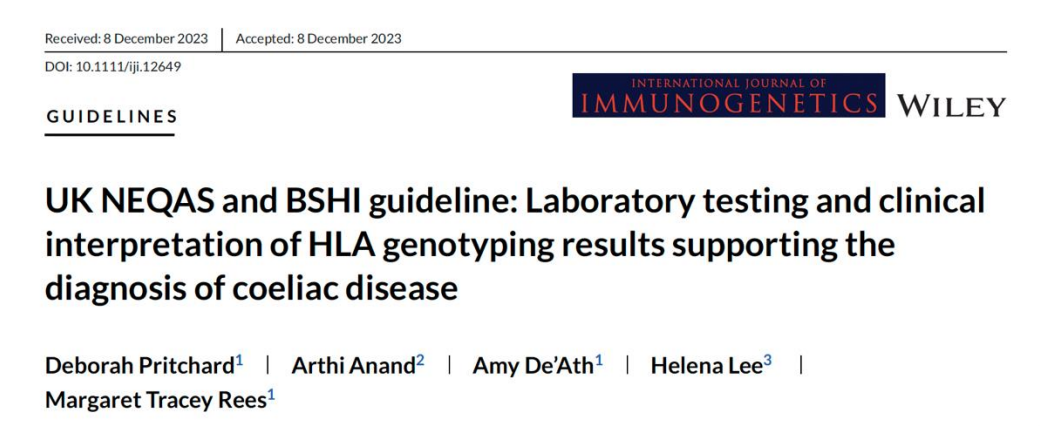






Pritchard, Deborah, et al. *International Journal of Immunogenetics* 51 (2024).

Standards for Reporting HLA Genotyping for Celiac Disease



Received: 8 December 2023 | Accepted: 8 December 2023
DOI: 10.1111/iji.12649

INTERNATIONAL JOURNAL OF IMMUNOGENETICS WILEY

GUIDELINES

UK NEQAS and BSHI guideline: Laboratory testing and clinical interpretation of HLA genotyping results supporting the diagnosis of coeliac disease

Deborah Pritchard[1] | Arthi Anand[2] | Amy De'Ath[1] | Helena Lee[3] | Margaret Tracey Rees[1]

Recommendations

Suggestions

HLA testing should **cover HLA-DQA1 and DQB1 loci**, and as a minimum, be able to detect the HLA alleles that make up the heterodimers **DQ2.5, DQ8 and DQ2.2.**

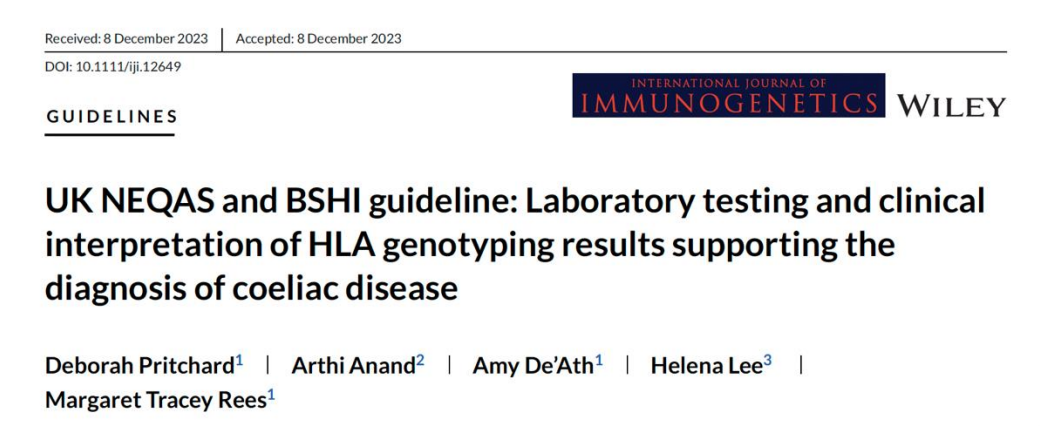
Reports should include **details of the methodology used** for testing, including any limitations of the assay impacting on interpretation of results.

Interpretative comments **may utilise shortened CD nomenclature (e.g., DQ2.5, DQ2.2)** in addition to official HLA nomenclature to aid clinician interpretation of results.

A simple summary statement for HLA results should be included in reports to aid clinical interpretation (e.g., the individual is positive for DQ2).

The report should include **a comment regarding utility of HLA typing results for CD diagnosis** (e.g., high negative predictive value/limited positive predictive value).

Risk Stratification for HLA Genotype is Not Straight Forward



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- **Scope:** 26 studies reviewed, spanning a wide range of geographic locations, sample sizes, and study designs.
- **Difficult to make conclusions:**
  - **Definitions:** varied genotype definitions and risk classification systems
  - **Population:** general and isolated populations limits generalizability
- **Consistent Finding: Individuals homozygous for HLA-DQ2.5 consistently had the highest risk** for developing celiac disease

Why does HLA-DQ2.5 have Greater Risk for CD?

Table 1. Peptide-binding registers, IC_{50} values, and T cell recognition of gluten epitopes in the context of HLA-DQ2.5 and HLA-DQ2.2

	Peptide-binding register, P1–P9									Binding/IC_{50}, μM		T cell stimulation	
Gluten epitope	1	2	**3**	4	5	6	7	8	9	DQ2.5	DQ2.2	DQ2.5	DQ2.2
Glia-α2	P	Q	**P**	E	L	P	Y	P	Q	15	130	+	–
Glia-α9	P	F	**P**	Q	P	E	L	P	Y	8	>500	+	–
Glia-α20	F	R	**P**	E	Q	P	Y	P	Q	30	>500	+	–
Glu-5	E	X	**P**	E	Q	P	Q	Q	F	100	>500	+	–
Glia-γ2	P	Y	**P**	E	Q	P	E	Q	P	65	350	+	–
Glia-γ1	P	Q	**Q**	S	F	P	E	Q	E	14	35	+	+
Glia-γ30	I	I	**Q**	P	E	Q	P	A	Q	10	50	+	+
Glt-17	P	F	**S**	E	Q	E	Q	P	V	25	12	+	+

Gluten Peptides

Position in the Peptide Groove

Binding IC_{50}

T Cell Stimulation

Subset of Gliadin epitopes **not presented by DQ2.2** compared to DQ2.5

Modern Diagnostic Algorithm

Requires patients to be on gluten while testing

Adult Patients

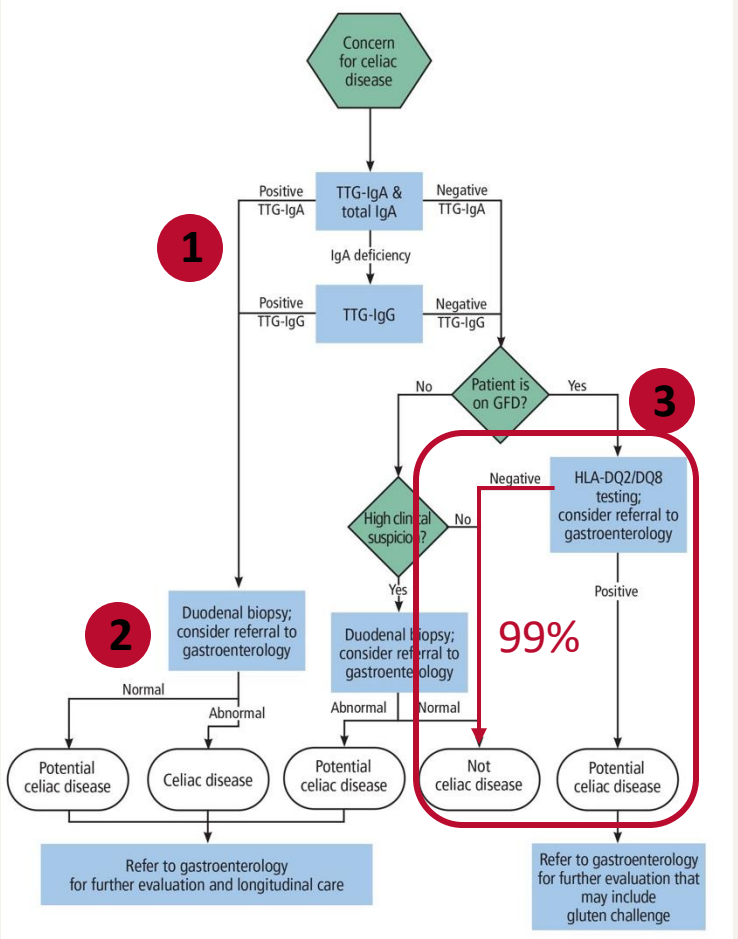
1. **Serology**: tTG-IgA + total IgA (to detect IgA deficiency)
   - EMA-IgA to confirm high pretest-probability or strong positives
2. **Duodenal biopsy:** Gold Standard
   - multiple biopsies (including bulb and distal duodenum)

Pediatric Patients Serology Only:
tTG-IgA ≥10× ULN confirmed by **EMA** in a second sample

What Role Does HLA Testing Play?

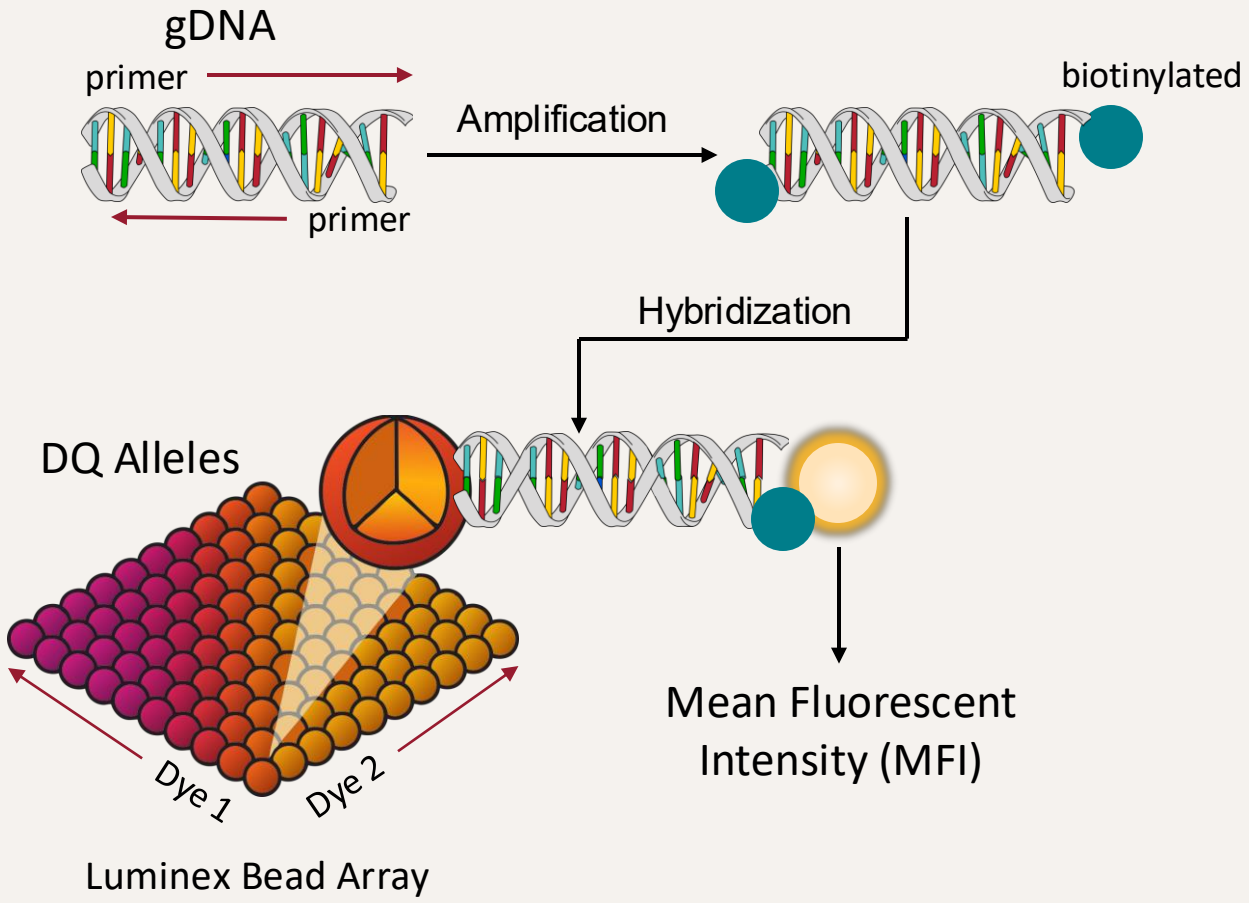
Use to **rule out** CD when results are equivocal or testing when patient is **on a gluten free diet**

Cleveland Clinic



How we Test and Report Results for Celiac Disease

Sequence-Specific Oligonucleotide (SSO)



Component	
DQB1*02 Interpretation	Negative | Positive (# of copies)
DQB1*03(8) Interpretation	Negative | Positive (# of copies)
DQA1*05 Interpretation	Negative | Positive (# of copies)

Narrative

Methodology comments:HLA-DQA1 and -DQB1 typing is performed using the reverse sequence specific oligonucleotide (r-SSO) method, which is based on an FDA approved IVD kit and validated by the BJH HLA laboratory.

Interpretive comments:DQB1*02 (DQ2) and DQB1*03 (DQ8) are present in 30-40% of the western Caucasian population, but only 3%...

Interpreting celiac disease reports

At Risk Individuals

1

Component	Greater Risk DQ2.5
DQB1*02 Interpretation	Positive (2 copy)
DQB1*03(8) Interpretation	Negative
DQA1*05 Interpretation	Positive (1 copy)

2

Component	
DQB1*02 Interpretation	Negative
DQB1*03(8) Interpretation	Positive (1 copy)
DQA1*05 Interpretation	Negative

3

Component	
DQB1*02 Interpretation	Negative
DQB1*03(8) Interpretation	Negative
DQA1*05 Interpretation	Positive (1 copy)

Patient from the 1st Slide
(**Not at risk**)

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Back to the patient case

Celiac Case

47-year-old woman with a history of schizophrenia, asthma, polyneuropathy, and migraines.

- **Surgical history:** Open abdominal wall reconstruction and parastomal hernia repair with mesh (2022).
- **GI presentation (2023):** >10 watery stools after meals, 15 lb unintentional weight loss, chronic gastroesophageal reflux (GERD) since surgery.

What should we order?

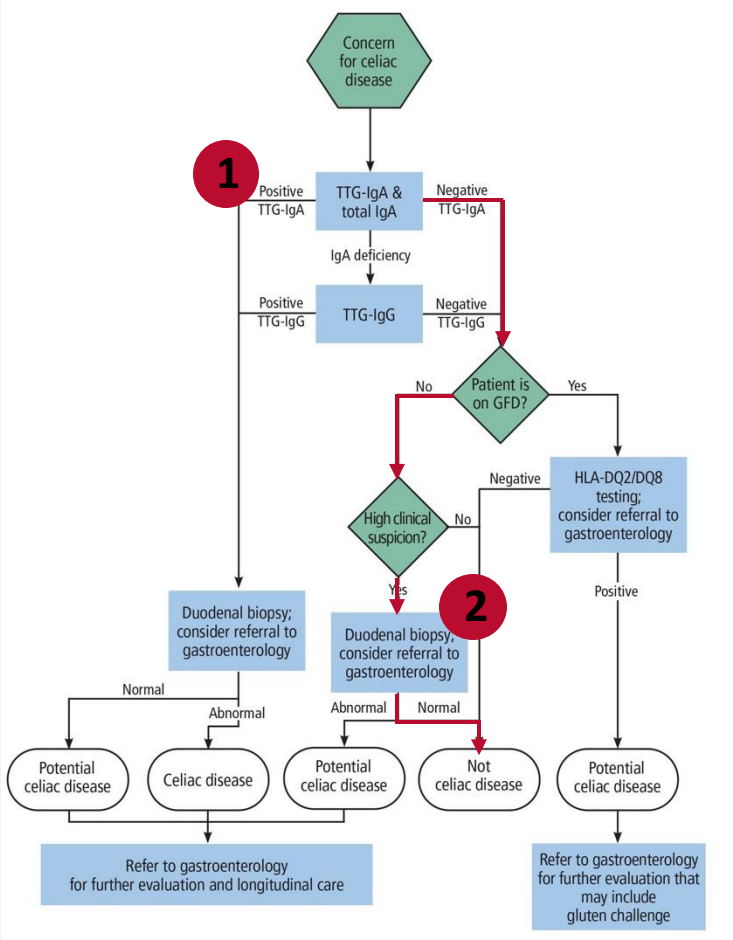
TTG-IgA	< 0.5 u/mL
Total IgA	145 mg/dL ref 70-400

Duodenal Biopsy

No Villous Blunting

2023 - Normal

2024 – Nodular Mucosa



Additional Work Up For the Patient

Outside of Conventional Workflow

HLA Typing

Component	
DQB1*02 Interpretation	Negative
DQB1*03(8) Interpretation	Negative
DQA1*05 Interpretation	Positive (1 copy)

Anti-Gliadin IgA < 0.5 u/mL

Immunogenic protein in gluten

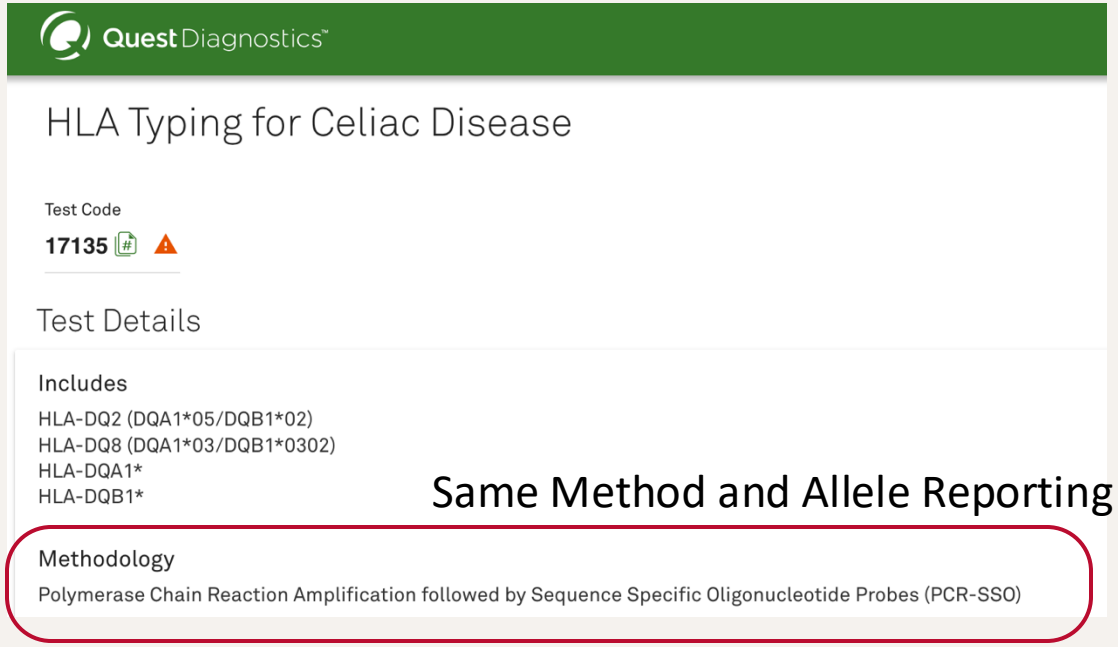
No Celiac Disease

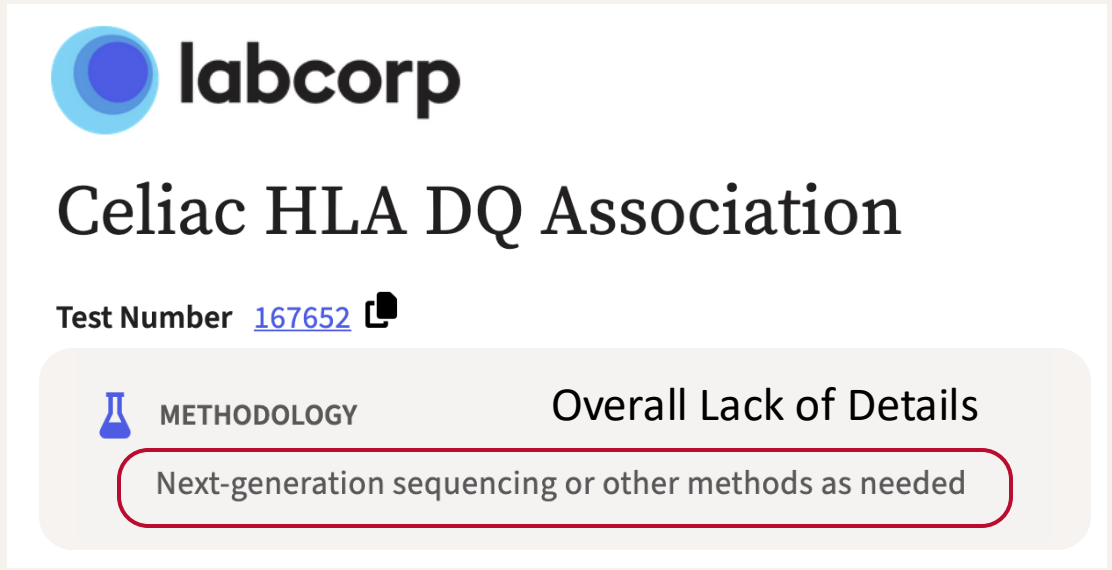
Is Our Testing Deficient?

The genetics testing indicates that you have a **positive HLA DQ A1*05** with **negative HLA DQ B1*02**, thus she does not have the full HLA type that would allow you to have celiac disease.

With that said, the **test that is done at BJC is not the best test (compared to LabCorp and Quest)**. However, his suspicion for celiac disease is very low based on the information given.

Here are his suggestions:
- request the biopsies to be reviewed by our pathologists here
- **check celiac HLA DQ via LabCorp** and also check tTG IgG and gliadin IgG at the same time.





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Pietzak, Michelle M., et al. Clinical Gastroenterology and Hepatology 7.9 (2009).

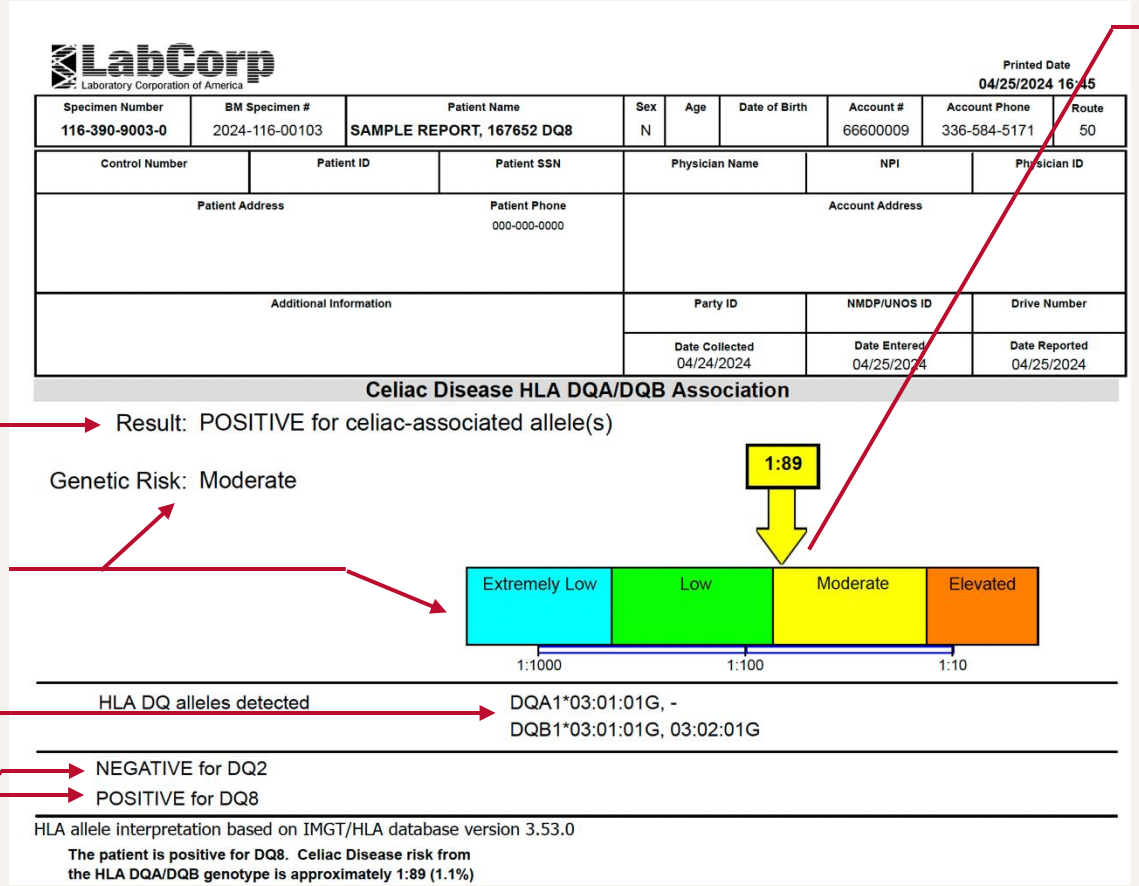
A Closer Look a LabCorp Reports

Overall Summary

Risk Stratification

Alleles

Risk Allele Differentiation



LabCorp
Laboratory Corporation of America

Printed Date 04/25/2024 16:45

Specimen Number	BM Specimen #	Patient Name	Sex	Age	Date of Birth	Account #	Account Phone	Route
116-390-9003-0	2024-116-00103	SAMPLE REPORT, 167652 DQ8	N			66600009	336-584-5171	50

Control Number	Patient ID	Patient SSN	Physician Name	NPI	Physician ID

Patient Address	Patient Phone	Account Address
	000-000-0000	

Additional Information	Party ID	NMDP/UNOS ID	Drive Number
	Date Collected 04/24/2024	Date Entered 04/25/2024	Date Reported 04/25/2024

Celiac Disease HLA DQA/DQB Association

Result: POSITIVE for celiac-associated allele(s)

Genetic Risk: Moderate

1:89

Extremely Low | Low | Moderate | Elevated

1:1000 1:100 1:10

HLA DQ alleles detected: DQA1*03:01:01G, -
DQB1*03:01:01G, 03:02:01G

NEGATIVE for DQ2
POSITIVE for DQ8

HLA allele interpretation based on IMGT/HLA database version 3.53.0

The patient is positive for DQ8. Celiac Disease risk from the HLA DQA/DQB genotype is approximately 1:89 (1.1%)

Risk Stratification

Genetic Risk from HLA-DQA/DQB Genotypes

DQ2 DQA1*05
DQB1*02
DQ8 DQA1*03
DQB1*03:02

Genotype	Risk
DQ2 + DQ8	1:7 (14.3%)
DQ2 + DQ2 OR DQ2 Homozygous *02	1:10 (10%)
DQ8 + DQ8	1:12 (8.4%)
DQ8 + DQB1*02	1:24 (4.2%)
Homozygous DQB*02	1:26 (3.8%)
DQ2 alone	1:35 (2.9%)
DQ8 alone	1:89 (1.1%)
Population risk (genotype unknown)	1:100 (1%)
1/2 DQ2: DQB1*02	1:210 (0.5%)
1/2 DQ2: DQA1*05	1:1842 (0.05%)
No HLA-DQA/DQB susceptibility alleles	1:2518 (<0.04%)

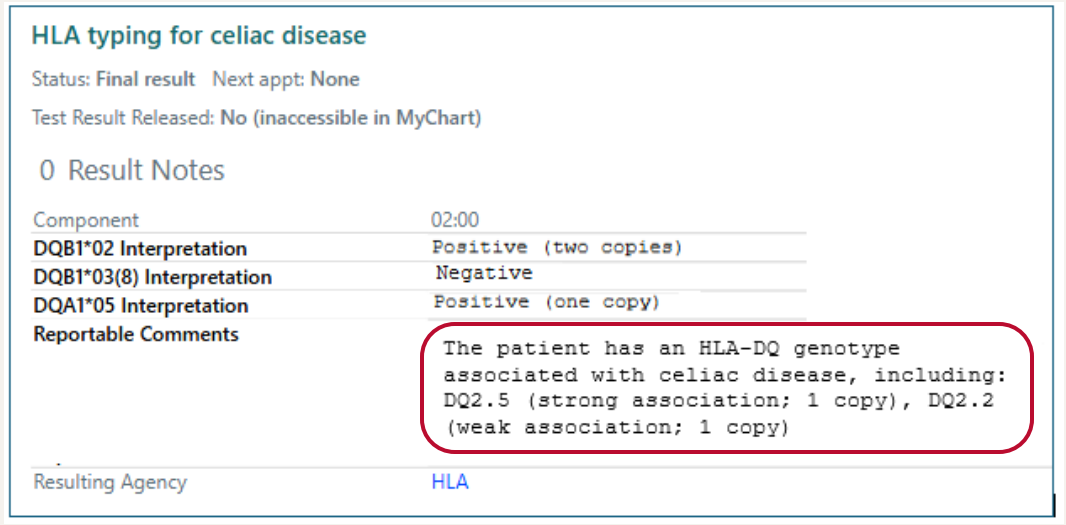
Caveat

Analysis done by Prometheus Labs

Logistic Regression Using
- HLA Genotype
- EMA-IgA Positivity

Not Confirmed Celiac Disease

Changes to Our Reporting



HLA typing for celiac disease

Status: Final result Next appt: None

Test Result Released: No (inaccessible in MyChart)

0 Result Notes

Component	02:00
DQB1*02 Interpretation	Positive (two copies)
DQB1*03(8) Interpretation	Negative
DQA1*05 Interpretation	Positive (one copy)
Reportable Comments	The patient has an HLA-DQ genotype associated with celiac disease, including: DQ2.5 (strong association; 1 copy), DQ2.2 (weak association; 1 copy)
Resulting Agency	HLA

Mockup from Rachel

HLA testing should **cover HLA-DQA1 and DQB1 loci**, and as a minimum, be able to detect the HLA alleles that make up the heterodimers **DQ2.5, DQ8 and DQ2.2.**

Reports should include **details of the methodology used** for testing, including any limitations of the assay impacting on interpretation of results.

Interpretative comments **may utilise shortened CD nomenclature (e.g., DQ2.5, DQ2.2)** in addition to official HLA nomenclature to aid clinician interpretation of results.

A simple summary statement for HLA results should be included in reports to aid clinical interpretation (e.g., the individual is positive for DQ2).

The report should include **a comment regarding utility of HLA typing results for CD diagnosis** (e.g., high negative predictive value/limited positive predictive value).

Conclusions

- Celiac disease is an immune-mediated disorder triggered by gluten peptides, causing both gastrointestinal and extraintestinal symptoms.
- **Diagnostic Algorithm:**
  1. **Initial evaluation** begins with serologic testing - *tissue transglutaminase IgA (tTG-IgA)* with *total IgA* to detect IgA deficiency.
  2. **Duodenal biopsy** is typically the next step, assessing for villous atrophy and mucosal changes.
  3. **HLA typing** is valuable as a **rule-out tool -** absence of HLA-DQ2 (2.2 or 2.5) and HLA-DQ8 has a very high negative predictive value.
     - **Best uses**: patients already on a gluten-free diet, unclear or discordant diagnostic results, or screening high-risk relatives.
     - **Testing method**: Performed via SSO analysis, reporting the presence and copy number of risk alleles.

References

- Lindfors, K., Ciacci, C., Kurppa, K. *et al.* Coeliac disease. *Nat Rev Dis Primers* 5, 3 (2019).
- Pietzak, Michelle M., et al. "Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles." *Clinical Gastroenterology and Hepatology* 7.9 (2009).
- Pritchard, Deborah, et al. "UK NEQAS and BSHI guideline: Laboratory testing and clinical interpretation of HLA genotyping results supporting the diagnosis of coeliac disease." *International Journal of Immunogenetics* 51 (2024).
- Vader, Willemijn, et al. "The HLA-DQ2 gene dose effect in celiac disease is directly related to the magnitude and breadth of gluten-specific T cell responses." *Proceedings of the National Academy of Sciences* 100.21 (2003).